VRDN-001, A Full Antagonist Antibody to the Insulin-Like Growth Factor-1 Receptor (IGF-1R) for Thyroid Eye Disease (TED): Phase 1/2 Proof of Concept in Patients with TED

Shoaib Ugradar[1] | Barrett Katz[2] | Denis O'Shaughnessy[2] | Rochelle Summerfelt[2] | Angela She[2] | Raymond Douglas[3]

[1]UCLA Stein Eye Institute, Los Angeles, CA; [2]Viridian Therapeutics, Waltham, MA; [3]Cedars Sinai Medical Center, Los Angeles, CA.

Poster #535

KEY TAKEAWAYS

We report the first TED cohort treated with **VRDN-001:**

- After only **2 infusions** of 10 mg/kg, subjects demonstrated clinically meaningful efficacy at 6 weeks.
- Rapid, marked improvements occurred in proptosis, diplopia, and inflammation, greater than those observed at the same time point in other RCTs employing anti-IGF-1R mAbs for TED.
- These results occurred with a favorable safety profile, with no serious AEs, hyperglycemia, or infusion reactions observed.

VRDN-001 may become a best-in-class treatment option.

INTRODUCTION AND METHODS

- **VRDN-001**, a full antagonist antibody to the IGF-1 receptor, is under development for the treatment of TED.
- Clinical and preclinical studies have confirmed IGF-1R antagonism can reduce the inflammation and proptosis that occur in TED.[1-4]
- Adult patients with active, moderate-to-severe TED presenting within 12 months of disease onset and a CAS of ≥4 were assessed for 6 weeks.
  - 8 subjects were randomized to 2 IV infusions 3 weeks apart of either 10 mg/kg **VRDN-001** or placebo (3:1)
  - Efficacy end points included proptosis responder rate (≥2 mm improvement), overall responder rate (≥2 mm improvement in proptosis and CAS improvement of ≥2), diplopia resolution, and change from baseline in proptosis and CAS
- We provide initial results from the first cohort of TED patients in our phase 1/2 RCT evaluating **VRDN-001** (NCT05176639).

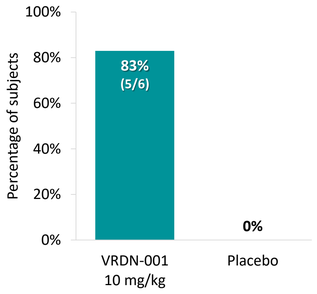
BASELINE CHARACTERISTICS

	VRDN-001 10 mg/kg (n=6)	Placebo (n=2)
Age, mean years (SD)	39 (5.2)	48 (11.5)
Female, n (%)	4 (67)	1 (50)
Proptosis, mean mm (SEM)	24.8 (1.2)	22.5 (4.5)
CAS, mean (SEM)	5.2 (0.3)	5.5 (1.5)
Diplopia on enrollment, n (%)	4 (67)	1 (50)
Diplopia, mean Gorman score (SD)[a]	2.0 (0.8)	3.0 (N/A)
Months since onset of TED signs/symptoms, mean (SEM)	7.3 (1.7)	11.9 (0.3)

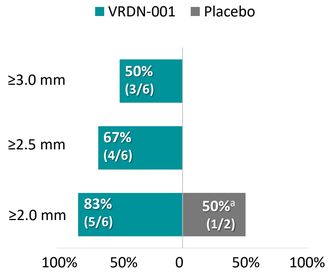
[a]Includes subjects with diplopia on enrollment.

EFFICACY RESULTS AT 6 WEEKS

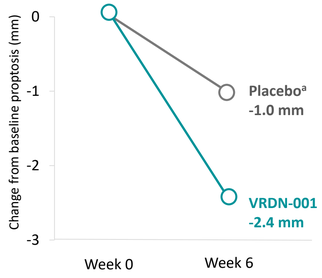
Overall responder rate



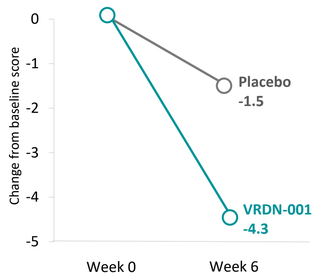
Proptosis responder rates



Mean proptosis change

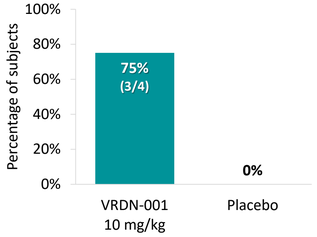


Mean CAS change



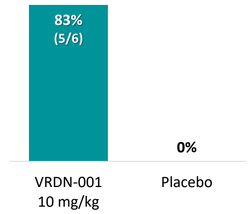
[a]1 of 2 placebo subjects showed reduction of exophthalmometer-measured proptosis (2 mm) but reported no change in CAS, and the proptosis reduction was not confirmed by MRI (which showed 0.58 mm worsening). Exophthalmometry results for VRDN-001-treated subjects were confirmed by MRI/CT imaging where available.

Diplopia resolution

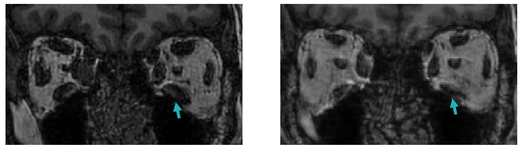


Diplopia at baseline: 4 of 6 in VRDN-001 group and 1 of 2 in placebo group

CAS decrease to 0 or 1



Pre/post treatment MRI scans in representative VRDN-001 responder



Baseline (Week 0) | After 2 VRDN-001 infusions (Week 6)

Coronal sections of orbital scans from one subject pre/post treatment. Blue arrows highlight reduction in size of the inferior rectus muscle.

Comparison of VRDN-001 efficacy results with previous RCTs for anti-IGF-1R antibodies in TED at 6 weeks

		Signs		Symptoms		
	Overall responder rate (reductions of ≥2 mm in proptosis and ≥2 points in CAS)	Proptosis responder rate (% with ≥2 mm reduction from baseline)	Mean proptosis change (Change from baseline)	CAS of 0 or 1 (% with no or minimal inflammation)	Mean CAS change (Change from baseline)	Diplopia resolution (% improved to a score of 0)
VRDN-001 10 mg/kg (n=6)	**83%**	**83%**	**-2.4 mm**	**83%**	**-4.3**	**75%**
Teprotumumab[3,5] 10 & 20 mg/kg (n=42, phase 2)	46%	55%	-1.8 mm	21%	-2.5	29%
Teprotumumab[4,5] 10 & 20 mg/kg (n=41, phase 3)	44%	56%	-1.9 mm	22%	-2.1	36%

- **VRDN-001** responses occurred rapidly and compared favorably with teprotumumab.
- **VRDN-001** is a more complete antagonist of IGF-1R (see Poster #132), potentially explaining its favorable clinical activity.

Poster #132

INTERIM SAFETY RESULTS

Previously reported AEs from IGF-1R blockade	VRDN-001 10 mg/kg (n=6)	Placebo (n=2)
Muscle spasms	2	0
Headache	1	1
Fatigue	1	2
Diarrhea	1	0
Hearing impairment	1	0
Alopecia	0	1
Nausea	0	0
Hyperglycemia	0	0
Dry skin	0	0
Dysgeusia	0	0
Infusion reactions	0	0

Data are through the week 6 visit of last patient. All but diarrhea and headache in the placebo subject were deemed treatment related by the masked investigator. Muscle spasms were mild and resolved without intervention. Hearing impairment was reported by subject as "ringing in the ears" and resolved within 2 weeks without intervention (audiometry was normal at all tested frequencies at next visit).

- AEs were mild (80%) or moderate (20%).
- No serious AEs, hyperglycemia, or infusion reactions occurred.

Disclosures: This study was sponsored by Viridian Therapeutics. VRDN-001 is an investigational treatment. Formatting and editorial assistance was provided by Keira Kim and funded by Viridian Therapeutics. All authors met the ICMJE authorship criteria and had full access to relevant data. BK, DOS, RS, and AS are employees of Viridian Therapeutics. SU and RD have consulted for, conducted studies funded by, or received honoraria for services provided to Viridian Therapeutics.

References: 1. Pritchard J et al. *J Immunol*; 170:6348–6354 (2003); **2.** Krieger CC et al. *J Clin Endocrinol Metab;* 100:1071–1077 (2015); **3.** Smith TJ et al. *NEJM;* 376:1748–1761 (2017); **4.** Douglas RS et al. *NEJM;* 382:4 (2020); **5.** FDA clinical review of Tepezza (BLA 761143).

PDF of poster: Scan QR code or visit https://qrcodes.pro/c07rkN

Abbreviations used in poster: mABs, monoclonal antibodies; IV, intravenous; RCT, randomized controlled trial; CAS, Clinical Activity Score; SD, standard deviation; SEM, standard error of mean; MRI, magnetic resonance imaging; CT, computed tomography; AE, adverse event.

Contact Information: info@viridiantherapeutics.com

Clinical Trial ID: NCT05176639

Poster #535